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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/292,723 04/15/99 READHEAD

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EXAMINER

HM22/0424

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ART UNIT

PAPER NUMBER

1632

DATE MAILED:

04/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/292,723

Applicant(s)

READHEAD ET AL.

Examiner

Jill Martin

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 February 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-62,75-82,94-101 and 107-117 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-62,75-82,94-101 and 107-117 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☒ The proposed drawing correction filed on 15 April 1999 is: a) ☐ approved b) ☒ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

Art Unit: 1632

Applicant's election of Group I, wherein the vertebrate species is mammal and wherein the source of the promoter DNA is mammal in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' Amendment filed February 9, 2001, (Paper No. 11) has been entered. Claims 63-74, 83-93, 102-106, and 118-132 have been canceled, and claims 1, 75, 94, and 107 have been amended. Claims 1-62, 75-82, 94-101, and 107-117 are pending and are under current examination.

Claim Objections

Claims 1-62, 75-82, 94-101, and 107-117 are objected to because of the following informalities: The claimed invention has not been amended to read on only the elected invention. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

Art Unit: 1632

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-62, 75-82, 94-101, and 107-117 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 135-149, 151, 157-163, 171, and 199 of copending Application No. 09/191,920. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets are directed to an *in vivo* method of incorporating a polynucleotide into a male vertebrate's germ cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-62, 75-82, 94-101, and 107-117 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 124-139 and 157-159 of copending Application No. 09/272,443. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets are directed to an *in vivo* method of incorporating a polynucleotide into a male vertebrate's germ cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art Unit: 1632

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-62, 75-82, 94-101, and 107-117 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for methods for obtaining selectable transgenic stem cells from transgenic pH CyclinA1-EGFP mice, does not reasonably provide enablement for methods and products encompassing any and all transgenic mammals comprising any and all stem cell-specific promoters operably linked to DNA encoding fluorescent or light-emitting protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to make or use the claimed invention. Each of the claims require transfection of male mammalian germ cells via administration to the gonad (as per the election of Paper No. 11).

The specification discloses that the invention arose from a desire to improve the production of transgenic animals. It is noted that the claims include the genetic modification of human germ cells for transfer into human or non-human germ cells. As the specification fails to teach how to make or use such genetically modified human germ cells, it is suggested that the claims be limited to “non-human” because germline gene therapy is an unpredictable and

Art Unit: 1632

undeveloped art on the basis that RAC of NIH will not consider any germ-line gene therapy protocols, and that people skilled in the art consider that the technology for human germ-line manipulation is too inefficient and too preliminary in its development for consideration. See page 79 of Gene Therapy, A Handbook for Physicians. Although the specification indicates that the method could be used potentially to correct genetic defects which cause infertility, the specification teaches no genetic sequence which functions to correct any fertility problem. In fact, no gene is known to date that would correct a fertility problem, much less be delivered via germline gene transfer.

The state of the art of making transgenic mammals is fairly established in regards to the methods where fertilized oocytes are microinjected or in mice where ES cells are used. The presently claimed method, wherein the sperm cells are transfected (via administration to a gonad) is not well-established and is unpredictable. The method has been tried in the past with varying degrees of success. Sato et al. (IDS) report that the system was unsuccessful in producing transgenic offspring. Lavitrano et al. (IDS) reported success in making transgenic offspring, but, as reported by Brinster et al. (No simple solution...) (IDS), the results were not repeatable. Later, in 1999, Chang et al. (IDS) report success in making transgenic rats using liposome-complexed DNA. It is not clear why the earlier reports were not successful in making transgenic offspring. Sato et al. speculate that the mode of transfection was the reason that their method was not successful. Applicant's preferred and exemplified method of transfection uses a stem cell-specific promoter construct, particularly human cyclin A1 promoter. Accordingly, in view of the

Art Unit: 1632

unpredictable state of the art, the claimed methods, cells, and mammals are enabled only for the transgenic mice comprising the human cyclin A1 promoter construct.

To this end, DNA associates tightly with spermatozoa such that demonstrations of presence of transfected cells in the testes or in ejaculate does not demonstrate that the germ cells were actually transfected. As such, it is not clear as to whether the sperm cells are more or less susceptible to transfection at particular stages. Because it is not known as to which, if any, types of sperm forming cells are transfected it is not clear as to how long transfected germ cells would remain in a particular animal. These parameters appear to be very important because the timing of the matings may need to be controlled by the duration of the transfected sperm cells.

Furthermore, the claims require the use of a stem-cell specific promoter, particularly human cyclin A1 promoter. The specification fails to teach that stem-cell specific transgene expression using any other promoter construct. It is well known in the art that the state of the transgenic art is unpredictable, particularly at the time of effective filing, even within the mouse system, with regard to transgene behavior and the resulting phenotypic effect. See Wall (Theriogenology, 1996) who reports that "our lack of understanding of genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph.

In conclusion, in view of the nature of the invention, the state of the prior art, the lack of predictability found in the art, the breadth of the claims, the lack of appropriate guidance, and the lack of correlatable working examples, it would require undue experimentation to make or use the

Art Unit: 1632

instant invention encompassing any and all transgenic mammals having any and all stem cell-specific promoters.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-62, 75-82, 94-101, and 107-117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, the limitations “germ cell” or “maturing germ cell” are vague and indefinite as to what is intended to be encompassed within the metes and bounds of the claims. In particular, it appears that the specification teaches transfection of germ cells within the testis or gonad and fails to define what is meant by a “mature” sperm cell. Clarification and/or amendment to the claims is requested.

In the claims, the limitation “at about or below the vertebrate’s body temperature and for a transfection-effective period of time” is vague and indefinite with regard to what is intended to be claimed. In particular, it is unclear as to what the limitation pertains or to what the limitation modifies, *i.e.*, gene delivery mixture, transfecting agent, transfecting, *etc.* Clarification and/or amendment to the claims is requested.

Art Unit: 1632

Conclusion

No claim is allowed.

The claims are free of the prior art of record because the prior art fails to teach techniques for transfecting germ cells via administration of a stem cell specific promoter construct to gonad.

However, these claims are subject to other rejections.

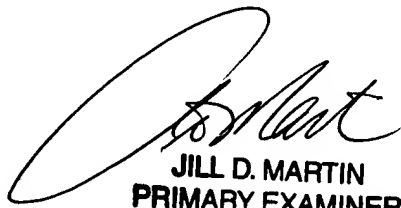
Art Unit: 1632

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jill Martin whose telephone number is (703)305-2147.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at (703)305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Kay Pinkney whose telephone number is (703)305-3553.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.



JILL D. MARTIN
PRIMARY EXAMINER

Jill D. Martin
Primary Examiner
Art Unit 1632